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A Model for Cellular Pattern Formation of Scales in a Butterfly Wing

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Abstract. The cellular pattern in a lepidopteran wing has two main characteristics. First, the scales of the wing form nearly straight parallel rows in the anteroposterior direction, and second, these rows are arranged at regular interval in the proximodistal direction. We investigated the mechanism of the cellular pattern formation by computer simulations in a two-dimensional discrete model. In comparison with experimental observations, we have obtained following results: 1) Lateral inhibition in scale cell differentiation should be working to form the uniformly distributed pattern of scale precursor cells. 2) The periodic cellular pattern in the wing can be formed by differential chemotaxis and/or position-specific differential cell adhesion. 3) In order to estimate the ratio of scale precursor cells to all the cells in the wing, it is necessary to account for size differences between the scale precursor cell and the undifferentiated epidermal cell.

1. Introduction

Spatial periodicity has been observed in the arrangement pattern of scales in a butterfly wing. In the pupal wing, scale precursor cells (SPC, for short) show the same arrangement pattern as do scales of the adult wing. This arrangement pattern of SPC provides a good example for the study of cellular pattern formation in multicellular organisms (Yoshida and Aoki, 1989).

Some basic ideas for the cellular pattern formation have been presented so far. Wolpert (1969) presented the positional information theory which says that a cell in a developing organism has a specific position relative to the other cells and is differentiated accordingly. On the other hand, it is known that in the cellular slime mold *Dictyostelium discoideum*, cells first differentiate into either prestalk or prespore cells independently of their positions in the organism, and then they form a typical cellular pattern by cell sorting (Forman and Garrod, 1977; Tasaka and Takeuchi, 1981). The recent development of molecular biology has revealed some molecular bases for pattern formation mechanisms (e.g. cAMP for the pattern formation of *D. discoideum* (Bonner, 1967); candidates of morphogens for hydra pattern formation

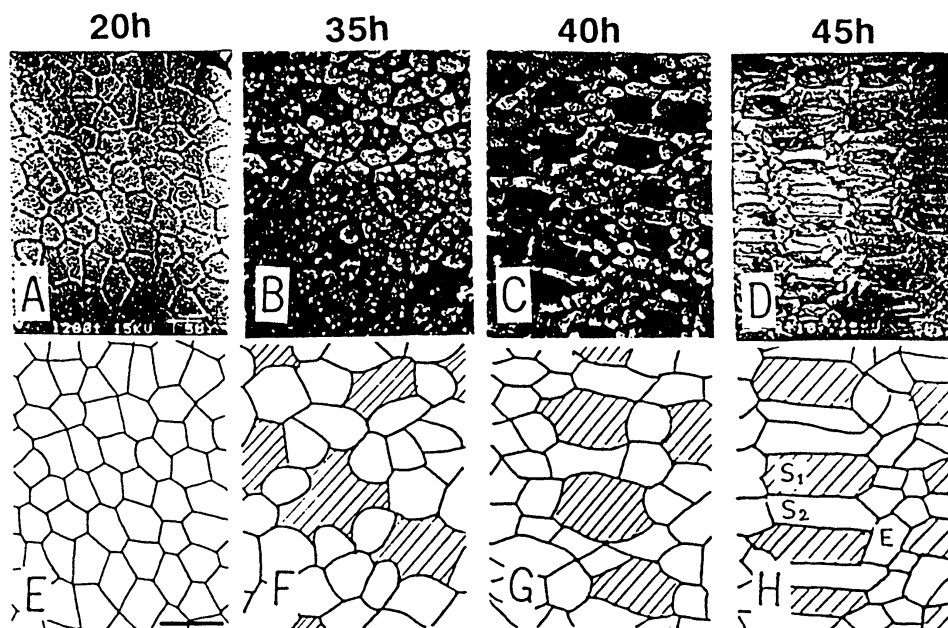


Figure 1. Formation process of the pattern of regularly spaced scale rows in a lepidopteran wing. A, B, C, and D indicate scanning electron micrographs of the pupal wing epidermis about 25 hr, 35 hr, 40 hr, and 45 hr after pupation, respectively. E, F, G, and H are figures traced out from the above photographs A, B, C, and D, respectively. S1 cells are drawn by oblique lines in these figures. The right direction of the figures is the distal direction of the wing, and the left is the proximal. These direction are the same in all the figures in this paper. The bar indicates a length of $10\mu\text{m}$.

(Schaller and Gierer, 1973; Berking, 1977); cell-cell adhesion molecules controlling animal morphogenesis (Edelman, 1984; Hatta et al., 1985; Takeichi, 1988)).

Little is known about the cellular and molecular bases for the cellular pattern formation in a lepidopteran wing. Based on some possible ideas which were partly presented by Yoshida (1989), we investigated the mechanism of the cellular pattern formation in the wing by computer simulations in a two dimensional discrete model. Our purpose in this paper is to search theoretically for what mechanisms should be working at each developmental stage in comparison with experimental observations. In the next section, we briefly summarize characteristics and processes of the formation of periodic scale rows in the wing. In section 3, we describe possible mechanisms for the pattern formation. In section 4, we present our model framework and basic assumptions. Section 5 is devoted to surveying the results by computer simulations of the model, and comparison with experimental observations. The last section is for a summary of the results and discussion.

2. Formation of Regularly Spaced Scale Rows

The formation of periodic cellular pattern of SPC proceeds as follows (Yoshida and

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Aoki, 1989; Yoshida, 1989): 1) The scale pattern develops first in the epidermis of the pupal wing. At about 25 hr after pupation, undifferentiated epidermal(E, for short) cells spread over the pupal wing to form a typical surface cell pattern(Figs.1 A,E). 2) E cells begin to differentiate into SPC, which we refer to as S1 cells. S1 cells are distributed randomly in space, and they form a uniform pattern of S1 cells(S1-UP, for short), in which S1 cells do not come in contact with each other(Figs.1 B,F). 3) S1 cells get longer in the proximodistal direction(Figs.1 C,G) and rearrange their positions. At the same time, another type of SPC(S2 cells, for short) appears next to S1 cells in the anteroposterior direction. Finally, we have the pattern of regularly spaced scale rows(RSSR, for short) composed of three kinds of cells: E, S1, and S2 cells(Figs.1 D,H).

3. Possible Mechanisms for the Cellular Pattern Formation

We describe possible mechanisms for the pattern formation of SPC, which have not always been established yet and must be tested both by experiments and theoretical analyses.

a) *Lateral inhibition(LI, for short) in scale cell differentiation*

LI means that a S1 cell produces an inhibiting substance, which prevents differentiation of new S1 cells in the nearest points. This kind of inhibition is also suggested in the cellular pattern formation of a grasshopper(Doe and Goodman, 1985) and a fruitfly(Campos-Ortega, 1988), and LI has been discussed in relation to S1-UP formation(Honda and Yoshida, 1987).

b) *Differential chemotaxis(DC, for short)*

DC means that cells react differentially to the concentration gradient of a chemical substance and they move accordingly. Although such a chemical substance has not been found yet, we assume that the substance originates from the basal part of the wing and diffuses over the whole wing to form the concentration pattern.

c) *Position-specific differential cell adhesion(PS-DCA, for short)*

Steinberg(1963) first proposed the "differential cell adhesion hypothesis(DCA)" to account for observed facts on cell self-sorting in cell aggregates. The hypothesis asserts that differential intercellular adhesiveness works among different types of cells, and cells automatically sort themselves out to maximize the total adhesion of cells. Recently, new light has been shed on the theory of cell adhesion from investigations of cell adhesion molecules (e.g. CAMs and Cadherins). We consider here PS-DCA as a possible mechanism in the cellular pattern formation of SPC: cell adhesion does not only depend on the difference in cell types, but also on the positions of cells in the wing(Nardi and Kafatos, 1976 a,b).

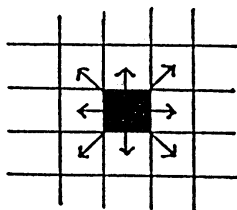


Figure 2. Eight possible directions of cell movement.

d) *Randomness in cell differentiation(RCD, for short) and randomness in cell movement(RCM, for short)*

Randomness referred here has two meanings. First, we mean randomness in positioning and timing in differentiation of S1 cells in the pupal wing. In this case, we assume implicitly that all the E cells tend to differentiate into S1 cells if there is nothing to inhibit the differentiation. We consider that this type of randomness RCD is indispensable for the formation of S1-UP. Second, we consider RCM as one of possible pattern formation mechanisms. This does not mean that cells move randomly to form a particular pattern, but that in cell rearrangement, some random factor of unknown origin works as a modifier to other directional movements such as those caused by chemotaxis and/or cell adhesion.

4. A Model for Cellular Pattern Formation of SPC

4.1 Outline of model

We consider three types of cells: undifferentiated epidermal E cells and scale precursor S1, S2 cells. Each cell is assumed to occupy a lattice point in a two dimensional domain. We first consider the situation, in which E cells occupy all the lattice points in the domain. E cells differentiate randomly in space into S1 cells (cf. RCD). After the formation of S1-UP, one of S1 cells is chosen randomly and it tries to move into one of the nearest eight lattice points. The selection of the direction(one out of eight) is done randomly (cf. RCM). If the motility condition is satisfied for the direction, the chosen S1 cell can move into the selected point (Fig.2). The cell movement is done by exchanging the two cells under consideration. We assume that after all the cell movements have been completed, S2 cells appear and locate next to S1 cells in the anteroposterior direction.

4.2 Lateral inhibition, chemotactic force, adhesion force, and motility condition

Each S1 cell has the nearest eight lattice points around it. LI means that S1 cell inhibits E cells from differentiating into S1 cells in the nearest points.

The chemotactic force acting on a cell is assumed to be proportional to the concentration gradient of chemoattractant at the cell. Different kinds of cells react differentially to the gradient. If we denote the concentration at a point (x, y) by

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$C(x, y)$, the chemotactic force F_c acting on a cell at (x, y) in a direction of (x', y') has the following expression:

$$F_c = R_c \frac{C(x', y') - C(x, y)}{\sqrt{(x' - x)^2 + (y' - y)^2}}, \quad (1)$$

where the coefficient R_c represents the sensitivity of the cell to the gradient and it depends on the cell type.

To evaluate PS-DCA, we next define the position-specific adhesiveness of a cell at a coordinate (x, y) to its four closest neighbors.

$$e(x, y) = \sum_{\substack{x'=x, y'=y\pm 1 \\ y'=y, x'=x\pm 1}} \lambda_{p(x,y)p(x',y')}(x, y), \quad (2)$$

where $p(x, y)$ denotes the cell type located at (x, y) and $\lambda_{ij}(x, y)$ indicates the affinity between i type cell at (x, y) and the neighboring j type cell. We note that the affinity $e(x, y)$ depends not only the cell types i and j , but also on the position (x, y) of the cell. The cell adhesion force F_a acting on a cell at (x, y) in a direction of (x', y') is assumed to be proportional to the difference of the adhesiveness under consideration:

$$F_a = R_a \{e'(x, y) + e'(x', y') - e(x, y) - e(x', y')\}, \quad (3)$$

where R_a is the adhesion coefficient and e' represents the adhesiveness for the pattern where the cells at (x, y) and (x', y') are exchanged.

We assume that a cell at (x, y) may move to the point (x', y') if and only if the motility condition:

$$F_c + F_a > 0, \quad (4)$$

is satisfied.

5. Computer Simulations and Results

5.1 The uniform pattern of S1 cells (S1-UP)

A typical cellular pattern caused by LI is shown in Fig.3. In a rectangular domain, a symbol "O" indicates a S1 cell, whereas a E cell is assumed to occupy a blank

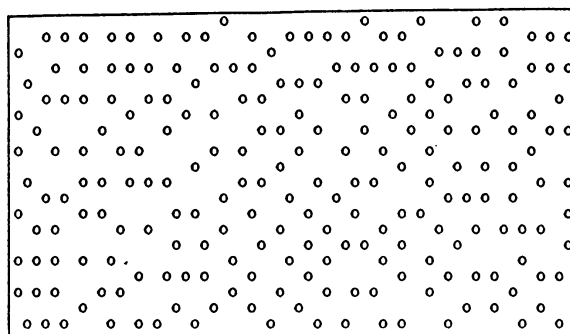


Figure 3. Uniform pattern of S1 cells caused by LI together with RCD in a rectangular domain. A symbol "O" indicates a S1 cell, whereas an E cell is assumed to occupy a blank lattice point " " in a two-dimensional discrete framework.

lattice point " ". RCD is also assumed in the calculations. We note that patterns of S1 cells by LI are similar to those of Figs.1 B,F, and that the ratio of S1 cells to all the cells(S1-RA, for short) is determined automatically, showing a fairly good matching with experimental data.

5.2 The pattern of regularly spaced scale rows(RSSR)

Starting from S1-UP discussed in Section 5.1, we investigate the cellular pattern formation caused by cell rearrangements. We assume following mechanisms for cell rearrangement: differential chemotaxis(DC) and position-specific differential cell adhesion(PS-DCA). Randomness in cell movement(RCM) is assumed in every case. We divide the cases into following two cases, in accordance with whether both mechanisms LI and RCD work or not after the formation of S1-UP. In each case, we have tested how mechanisms DC and/or PS-DCA affect the cellular pattern formation.

5.2.1 The case of both LI and RCD working still after S1-UP formation

In this case, an E cell could differentiate into a S1 cell when the lattice point gets free from inhibition of other S1 cells by cell rearrangement.

Patterns caused by DC

Figs.4 (a),(b), and (c) show a typical pattern formation process and the final cellular pattern by DC in a rectangular domain, where the concentration of chemoattractant is assumed to decrease monotonically from left(proximal) side to right(distal) side. We see that the cellular pattern reproduces the periodicity in the pattern of RSSR (cf.Figs.1 D,H). In these figures, a symbol "O" indicates a S1 cell, and a symbol "I" is a S2 cell, which is adjacent to S1 cell in the up(anterior) and down(posterior) direction, whereas blank lattice " " is occupied by a E cell. S1-NR in this case is about 25 %, which is somewhat larger than the observed data of about 17 % (Yoshida and Aoki, 1989).

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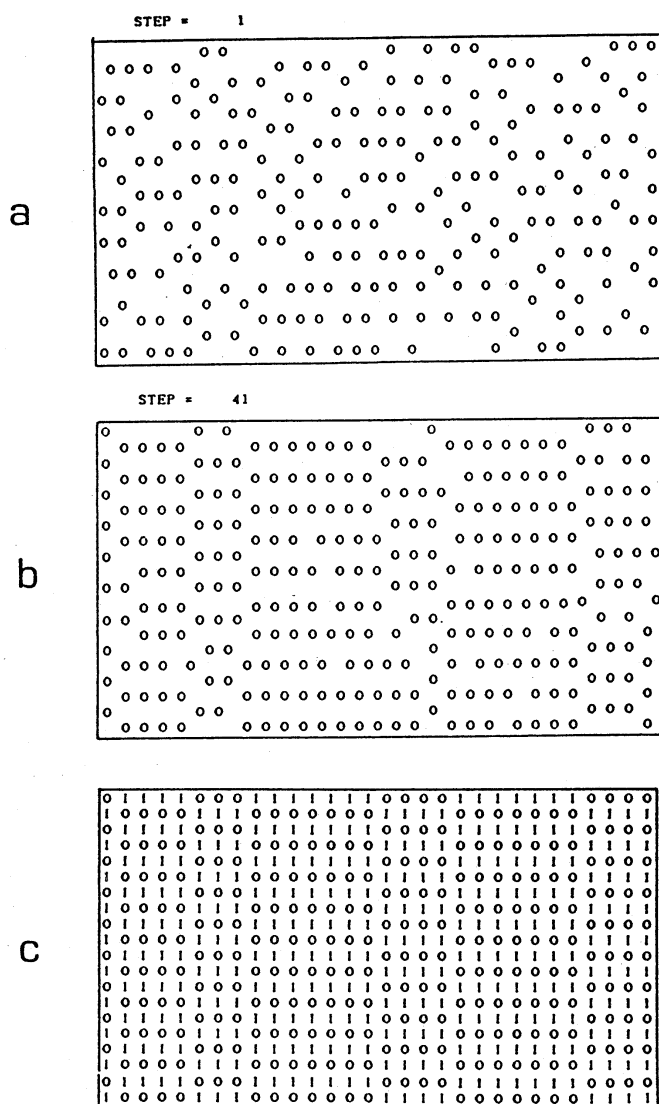


Figure 4. Formation process of RSSR via cell arrangement caused by DC in a rectangular domain. LI and RCD are also assumed in the simulation. According to the time course of simulations, Figures 4 (a), (b), and (c) indicate the uniform pattern of S1 cells, an intermediate cellular pattern, and the final regular pattern of S1 cells, respectively. A symbol "O" and a blank " " indicate a S1 cell and an E cell, respectively. A symbol "I" in the final cellular pattern(Fig.4 (c)) indicates a scale precursor S2 cell. The concentration of hypothetical chemical substance is assumed to decrease from the left(proximal) side to the right(distal) side in the rectangular domain.

Patterns caused by PS-DCA

PS-DCA can reproduce the pattern of RSSR as well as the case of DC. The obtained cellular pattern(not shown here) is very similar to Fig.4 (c) by DC. In addition to the differential cell adhesion among different types of cells, we have assumed the gradient of cellular adhesiveness decreasing from the left(proximal) side to the right(distal) side in a rectangular cellular domain.

In the case of both DC and PS-DCA working together, the pattern of RSSR is regenerated more quickly than either the case of DC or PS-DCA. In the present situation, we can not conclude which mechanism(DC or PS-DCA) is major for the cellular pattern formation of RSSR.

5.2.2 The case of neither LI nor RCD working after S1-UP formation

In this case, E cells cease to differentiate into S1 cells and S1-RA continue to be constant until the final cellular pattern is formed by cell rearrangement.

Patterns caused by DC

Since there is nothing to stop the cell movement toward the higher concentration of chemoattractant, DC causes S1 cells to move into the source region of the chemoattractant and forms segregated cellular patterns of S1 cells and E cells, which have not been observed in a lepidopteran wing.

Patterns caused by PS-DCA

If we choose the affinity parameters between adjacent cells suitably, a regularly spaced cellular pattern may be formed in the proximal region in the rectangular domain. In the distal region, however, there are no S1 cells because S1-NR continues to be constant. As a result, we have a semi-regular cellular pattern, in which S1 cells are distributed only in the proximal region, whereas the distal region is occupied by E cells.

6. Summary and Discussion

By use of a two-dimensional discrete model, we have tested how possible mechanisms (e.g. LI,DC,PS-DCA,...) should be working for the pattern formation of RSSR in a lepidopteran wing. We summarize obtained results as follows:

- 1) *In the formation of S1-UP in the pupal wing, LI should be working together with RCD.*
- 2) *The cellular pattern of RSSR in the wing may be formed via cell rearrangements caused by mechanisms DC and/or PS-DCA. In each case, S1-UP is assumed to have been already formed in the pupal wing before cell rearrangements occur.*
- 3) *S1-NR is evaluated by accounting for size difference among three kinds of cells(i.e.S1,S2,and E cells).*

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It is known that a given cell in a moth wing forms intimate contacts not only with adjacent cells but also with nonadjacent cells (Nardi and Magee-Adams, 1986). Besides chemotaxis and short-range cell adhesion, we would like to test the possibility of such long-range interactions among cells as a candidate of mechanisms for the cellular pattern formation in our model.

As noted above, there remains ambiguity in the mechanism for the cellular pattern formation of RSSR, which we have to make clear by further examinations including cooperative studies between theoretical analyses and experiments (e.g. grafting experiment). We are now improving our model within two-dimensional discrete model, without changing the main framework and idea. The model contains the shape and size difference among different kinds of cells, which has not been accounted for in the present model. We would like to present the fully detailed paper elsewhere in future.

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